Br. J. clin. Pharmac. (1991), **31**, 15–24 ADONIS 030652519100002X

A population study of the pharmacokinetics of felodipine

E. BLYCHERT[1,3], B. EDGAR[1,3], D. ELMFELDT[2,3] & T. HEDNER[1]
[1]Department of Clinical Pharmacology and [2]Internal Medicine, Sahlgrenska University Hospital, Göteborg, Sweden and [3]Cardiovascular Research, AB Hässle, Mölndal, Sweden

1 The pharmacokinetics of felodipine was studied after continuous oral administration of 5 or 10 mg conventional tablets to a population of 140 male and female Caucasian subjects, of which 67 were hypertensive patients and 73 were healthy volunteers. In addition, 42 of these individuals received felodipine intravenously.

2 With increasing age the area under the felodipine plasma concentration *vs* time curve (AUC), the maximum plasma concentration (C_{max}), and the terminal elimination half-life of felodipine increased, while the plasma clearance of felodipine decreased. The bioavailability and steady state volume of distribution and the time to C_{max} were not consistently influenced by age.

3 The ratio of the AUC of the primary pyridine metabolite of felodipine and that of unchanged drug decreased with increasing age.

4 Neither C_{max}, AUC nor the half-life of felodipine were related to body mass index.

5 The distribution of AUC for felodipine, as well as the ratio of the AUC of the first metabolite to that of unchanged felodipine, was unimodal. Thus, the presence of a sizable group of individuals, with a clinically significant different metabolism of 1,4-dihydropyridine due to genetic factors is unlikely.

6 The pharmacokinetics of felodipine did not seem to differ between hypertensive patients and healthy volunteers, when adjusted for age. Neither was there a difference between patients taking β-adrenoceptor antagonists and those who did not.

7 As a group the elderly had higher total concentrations of unchanged felodipine in plasma compared with younger individuals. The variation in plasma concentrations of felodipine between individuals is, however, only partially explained by age. In clinical practice this emphasizes the need for dose titration of felodipine.

Keywords felodipine population study pharmacokinetics age

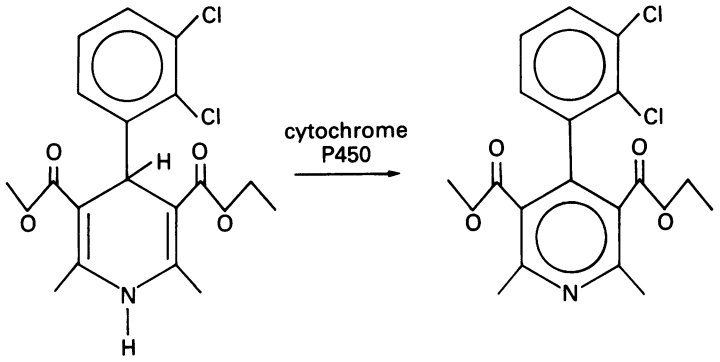
Introduction

The measurement of plasma concentrations of drugs in large numbers of individuals allows the study of differences in pharmacokinetics with regard to age, genetic, environmental, physiological or pathophysiological influences. Such factors are usually difficult to evaluate from conventional pharmacokinetic studies which usually include small numbers of patients and are restricted to homogeneous groups of individuals. By pooling data from pharmacokinetic studies of similar design, using identical analytical procedures, it is possible to obtain a large enough population for these evaluations.

Antihypertensive drugs are given to large sections of the population in most societies. Apart from potential genetic and environmental differences, other factors such as age, organ damage and concomitant drug therapy might influence both their pharmacokinetics and their antihypertensive effect.

Calcium antagonists are increasingly used in the management of hypertension, and this group of drugs is now considered to be one of the first line treatment alternatives along with diuretics, β-adrenoceptor antagonists and angiotensin converting enzyme inhibitors (Joint National Committee, 1988; WHO/ISH Guidelines 1989). Felodipine is a 1,4-dihydropyridine calcium antagonist for which a plasma concentration-effect relationship has been established (Blychert *et al.*, 1990; Edgar *et al.*, 1987). In man felodipine undergoes extensive first-pass metabolism (Edgar *et al.*, 1985a; Regårdh *et al.*, 1989), the major metabolic step involving oxidative degradation by cytochrome P450 IIIA of the 1.4-dihy-

Correspondence: Dr Eva Blychert, Department of Clinical Pharmacology, Sahlgrenska Hospital, S-431 45 Göteborg, Sweden



Felodipine

First metabolite of felodipine (dehydrofelodipine)

Figure 1 Pathways involved in the initial metabolism of felodipine. The rate-limiting step is the oxidation to dihydropyridine. All metabolites are pharmacologically inactive.

dropyridine to the inactive dehydrofelodipine (Figure 1, Bäärnhielm *et al.*, 1984; Hoffman & Andersson, 1984).

The metabolism of felodipine as well as other dihydropyridines has been shown to differ substantially between individuals (Regårdh *et al.*, 1990). Firstly, there is an age-related decrease in metabolism (Robertson *et al.*, 1987), which may be due to a reduction in hepatic blood flow or a decrease of intrinsic clearance, or both. Secondly, the possibility of a genetic polymorphism in the metabolism of 1,4-dihydropyridines has been discussed (Kleinbloesem *et al.*, 1984; Renwick *et al.*, 1988).

The present population study was undertaken in order to evaluate to what extent the pharmacokinetics of felodipine are influenced by demographic variables such as age, body mass index or concomitant antihypertensive therapy. In addition, we also investigated whether there was any evidence for a polymorphism in the pharmacokinetics of felodipine in the population selected.

Methods

Study population

The study was based on pharmacokinetic data obtained from 140 Caucasian subjects taking part in ten separate studies in Sweden and the United Kingdom. Each study included between 10 and 18 subjects and was approved by the regional ethics committee, as well as the isotope committee when radio-labelled felodipine was used.

Healthy subjects (n = 73) and hypertensive patients (n = 67) were included in the study. Most of the study population was male (n = 126) and only 14, all hypertensive patients, were female, since only women without child-bearing potential were eligible for participation. A wide age range, 20–80 years, was represented in the pooled material. The healthy subjects did not receive any concomitant medication, while the majority of hypertensive patients were also on other antihypertensive regimens. Twelve patients took a diuretic, 11 a β-adrenoceptor antagonist and 21 a combination of the two. Individuals suspected of drug or alcohol abuse were excluded. Table 1 gives a summary of the subject/patient characteristics for the whole population (n = 140) as well as for the age groups 20–39, 40–59 and 60–80 years.

Inclusion criteria for accepting healthy subjects into the studies were: Males between 20 and 40 years of age, except when specifically studying the the elderly (65–80 years). Subjects with concomitant diseases or allergic problems were excluded, as were subjects who had taken any prescription drugs during the 4 weeks preceding the study.

The criteria for including hypertensive patients in the studies were as follows: Males and women without child-bearing potential, 25–70 years of age with a documented diastolic blood pressure > 95 mm Hg on several occasions. Patients with severe angina pectoris, or clinically significant renal or liver function impairment were excluded, as were patients who had had a recent myocardial infarction.

Methodological considerations

The plasma concentration of felodipine is linear with dose in the range used (Edgar *et al.*, 1987). This justified the pooling of data from individuals receiving different doses, after normalising for dose.

Blood sampling, preparation of plasma, analysis of unchanged felodipine and its primary metabolite followed identical protocols in all studies. All samples were analysed by the same laboratory (AB Hässle, Mölndal, Sweden).

In figures where individual data are presented, different symbols have been used for the healthy subjects and the hypertensive patients. No direct comparisons between the two groups were made owing to the low number of hypertensive patients below the age of 40 years and the small number of healthy subjects above 40 years of age. Moreover, because of the exclusion criteria, there were virtually no women among the healthy subjects or in the two younger age groups of hypertensive patients.

Concomitant antihypertensive therapy, in particular β-adrenoceptor antagonists, which may reduce liver blood flow (Weiss *et al.*, 1978) might influence the metabolism of felodipine. Therefore, patients receiving β-adrenoceptor antagonists were analysed as a separate group.

There were very few patients with diagnoses other than hypertension in our population. Thus, no conclu-

Table 1 Subject/patient characteristics. Mean ± s.d. and median (in brackets) are given where appropriate

Age range (years)	n	*Age (years)*	*Body weight (kg)*	*BMI ($kg\ m^{-2}$)*	*Number of subjects/ patients*	*Number of subjects/patients with i.v. data*	*Number of patients with additional treatment*
20–80	140	43 ± 19 (39)	79 ± 13 (76)	25 ± 4 (24)	73/67	12/30	D = 12 B = 11 D + B = 21
20–39	70	26 ± 4 (24)	76 ± 8 (75)	23 ± 2 (23)	64/6	12/5	D = 0 B = 0 D + B = 1
40–59	30	52 ± 6 (54)	88 ± 15 (86)	28 ± 4 (27)	0/30	0/12	D = 8 B = 4 D + B = 11
60–80	40	68 ± 6 (67)	77 ± 15 (73)	27 ± 4 (26)	9/31	0/13	D = 4 B = 7 D + B = 9

D = Diuretics
B = β-adrenoceptor antagonist
D + B = Diuretics + β-adrenoceptor antagonists
BMI = Body mass index

sions can be drawn about the possible influence of other diseases on felodipine kinetics.

Dosage

A conventional tablet formulation of felodipine was used. Forty-four of the subjects/patients were given a 5 mg dose twice daily and the remaining individuals received 10 mg twice daily. The duration of treatment varied from 6 to 30 days. Thus all measurements were taken under steady state conditions. On study days the tablets were given in the morning at the clinical laboratory or out-patient unit after an overnight fast. The tablets were taken with at least 100 ml water.

Intravenous felodipine was given either as a 30 min infusion of 1.5 mg felodipine on a separate experiment day (n = 19) or as a 5 min infusion of 0.04 mg [^{3}H]-felodipine simultaneously with the oral dose (n = 23).

Blood samples

During the 12 h dosage interval, frequent blood samples were drawn into heparin tubes from an indwelling cannula in a forearm vein. In addition, in studies in which the terminal elevation half-life of felodipine was estimated, blood samples were also taken at 24 h or more after dosage. Samples taken more than 12 h apart were obtained by separate venepuncture. After sampling, the blood was cooled to room temperature and centrifuged at 3000 rev min^{-1} for 10 min. The plasma was stored frozen at −20° C until analysis.

Analysis of felodipine and its primary metabolite

The plasma concentrations of felodipine and its primary metabolite (dehydrofelodipine) were measured by gas chromatography with electron capture detection after extraction with toluene (Ahnoff, 1984; Ahnoff *et al.*, 1987). The method is selective and interference from endogenous plasma substances is low.

The lower assay limit of felodipine, i.e. the concentration giving a relative standard deviation of less than 15%, ranged from 0.5–2.0 nM. For the metabolite this limit was 2 nM. The within-run relative standard deviation of spiked plasma samples was 4–8% at 2 nM and 2–4% at 40 nM. The between-run reproducibility was approximately 5% at a concentration of 25 nM.

Statistical analyses

The influence of age was tested using one-way analysis of variance with age group as a factor. The following age groups were defined: 20–39 years, 40–59 years, 60–80 years. Mean and standard deviations are given throughout. In addition median values are given for the pharmacokinetic variables.

Calculations and abbreviations

Calculations of pharmacokinetic variables were made as indicated below. Plasma samples below the assay limit were treated as missing data in the kinetic and statistical calculations. Of the approximately 1500 blood samples taken 1% were missing or had drug concentrations below the assay limit.

$AUC_{p.o.}$ = area under the plasma concentration *vs* time curve after oral administration. The AUC for the dosage interval was calculated as AUC (0,12 h), using the linear trapezoidal method.

$AUC_{i.v.}$ = AUC after intravenous single dose administration = AUC(0,12) + AUC(12,∞), AUC(0,12) was calculated using the linear trapezoidal rule.

$AUC(12,\infty) = \frac{C(12)\cdot t_{½}}{\ln 2}$ where $C(12)$ is the plasma concentration measured 12 h after dose

b.i.d. = twice daily

C_{max} = maximum plasma concentration

C_{min} = trough plasma concentration, 12 h after dosage

CL = plasma clearance, calculated from dose/$AUC_{i.v.}$

D = dose

i.v. = intravenous administration

p.o. = oral administration

F = systemic availability $= \frac{D_{i.v.} \times AUC_{p.o.}}{D_{p.o.} \times AUC_{i.v.}}$

t_{max} = time of maximum plasma concentration

$t_{½}$ = terminal elimination half-life after the oral dose estimated from the slope of the log plasma felodipine concentration *vs* time curve. Data points from 8 h after dosage were used.

V_{ss} = steady state volume of distribution $= \frac{D_{i.v.} \times AUMC}{(AUC)^2}$ where AUMC is the area under the concentration-time *vs* time curve.

Results

Plasma concentrations vs *time*

The mean plasma felodipine concentration *vs* time curves during a dosage interval in the three age groups, after normalization to a 10 mg dose, are shown in Figure 2. Mean drug concentrations increased with age. The concentration of felodipine 2 h after dosing was 13.0 ± 7.3 nM in the young group, 16.0 ± 8.5 nM for the individuals aged 40–59 years and 21.1 ± 9.3 nM in subjects > 60 years. Trough concentrations 12 h after dose were 2.7 ± 1.6, 5.0 ± 3.2 and 7.0 ± 4.2 nM for the three groups, respectively. The peak to trough variation during a dosage interval was similar in each age group.

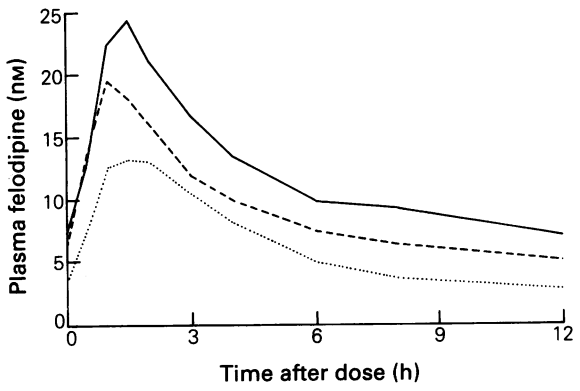


Figure 2 Mean plasma concentrations of felodipine (CpF) *vs* time during a dosage interval (10 mg twice daily) in the age groups 20–39 (·····, n = 70), 40–59 (---, n = 30) and 60–80 years (——, n = 40).

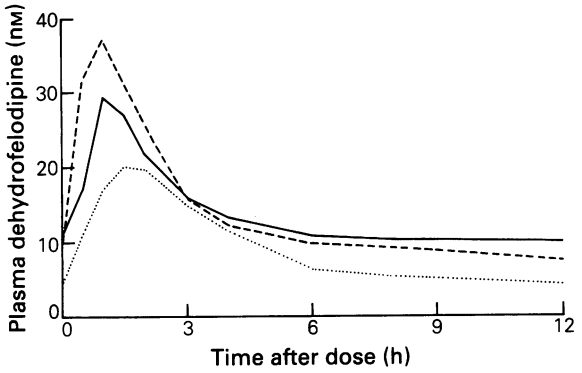


Figure 3 Mean plasma concentrations of dehydrofelodipine (CpM), first metabolite of felodipine, *vs* time during dosage interval (10 mg twice daily) in the age groups 20–39 (·····, n = 51), 40–59 (---, n = 28), and 60–80 years (——, n = 39).

The plasma concentration-time curves of dehydrofelodipine are shown in Figure 3. The mean concentrations of dehydrofelodipine 2 h after dose were 19.7 ± 8.2, 25.8 ± 14.4 and 21.7 ± 9.4 nM in order of increasing age. The concentration 12 h after dose, i.e. at trough, was lowest in the youngest and highest in the oldest group (4.2 ± 1.3, 7.4 ± 5.7 and 9.9 ± 4.6 nM, respectively).

Absorption

Table 2a summarizes pharmacokinetic variables for the whole population and for the different age groups. Table 2b gives P values for the comparisons between age groups for these variables.

The peak plasma concentration of felodipine increased with age (Figure 4). The mean peak concentration, C_{max}, was 30 ± 13 nM for the elderly while the young group had a mean peak concentration of 19 ± 9 nM. As shown in Figure 4, however, several young individuals had as high or higher plasma concentrations of felodipine as some of the elderly subjects. The distribution of C_{max} (Figure 4b) was skewed, but did not show any bimodality.

Although there was a slightly shorter time to peak concentration (t_{max}) in the group aged 40–59 years, there was no consistent change in t_{max} with age.

The systemic availability of felodipine (F), evaluated in the 42 subjects/patients who received i.v. felodipine in addition to oral treatment ranged from 4.4 to 36.2% (mean 14.5 ± 7.5%). The availability did not differ between the age groups (Table 2).

Distribution

The steady state volume of distribution (V_{ss}), determined after the i.v. dose did not vary with age (Figure 5, Table 2).

Elimination

Half-life Figure 6 shows the distribution of the terminal elimination half-life in relation to age indicating an inter-

Table 2a) Felodipine steady state pharmacokinetic variables for the whole population and for different age groups. Minimum (C_{min}), maximum (C_{max}) and time to maximum (t_{max}) plasma drug concentration and the area under the plasma drug concentration *vs* time curve (AUC), the steady state volume of distribution (V_{ss}), the terminal half-life ($t_{½}$), bioavailability (F), plasma clearance (CL) and the ratio dehydrofelodipine/felodipine (ratio D/F) are given. Data are normalized to a dose of 10 mg twice daily. Mean, s.d. and median (in brackets) are given.

	t_{max} (h)	C_{max} (nM)	C_{min} (nM)	V_{ss} ($l\,kg^{-1}$)	AUC (nM h)	$t_{½}$ (h)	Ratio D/F	F (%)	Clearance ($ml\,min^{-1}$)
	$n = 140$	$n = 140$	$n = 140$	$n = 42$	$n = 140$	$n = 118$	$n = 65$	$n = 42$	$n = 42$
All	1.4	23.1	5.0	9.2	100.9	23.1	1.42	14.5	655
	±0.7	±11.4	±3.6	±3.2	±53.2	±10.4	±0.38	±7.5	±285
	(1.5)	(21.0)	(4.2)	(9.0)	(88.5)	(21.9)	(1.47)	(13.1)	(620)
Age groups									
	$n = 70$	$n = 70$	$n = 70$	$n = 17$	$n = 70$	$n = 51$	$n = 27$	$n = 17$	$n = 17$
20–39 years	1.5	19.1	3.2	9.9	74.6	18.4	1.55	13.6	821
	±0.8	±9.0	±1.7	±3.4	±34.2	±10.1	±0.26	±9.0	±325
	(1.5)	(17.0)	(2.8)	(9.4)	(66.5)	(15.6)	(1.54)	(12.6)	(860)
	$n = 30$	$n = 30$	$n = 30$	$n = 12$	$n = 30$	$n = 28$	$n = 18$	$n = 12$	$n = 12$
40–59 years	1.2	23.3	6.1	9.3	110.2	23.8	1.49	13.9	644
	±0.6	±10.1	±3.4	±3.9	±55.3	±8.5	±0.39	±6.2	±145
	(1.0)	(23.0)	(5.3)	(7.1)	(103.5)	(24.5)	(1.50)	(14.3)	(652)
	$n = 40$	$n = 40$	$n = 40$	$n = 13$	$n = 40$	$n = 39$	$n = 20$	$n = 13$	$n = 13$
60–80 years	1.5	30.0	7.3	8.6	140.1	28.7	1.20	16.3	448
	±0.6	±12.9	±4.5	±2.7	±53.7	±9.3	±0.44	±6.5	±176
	(1.5)	(25.6)	(5.8)	(7.4)	(132.2)	(27.0)	(1.09)	(13.5)	(448)

Table 2b) *P* values for the analyses of variance comparing the pharmacokinetic variables in the three age groups

Comparison	t_{max}	C_{max}	C_{min}	V_{ss}	AUC	$t_{½}$	Ratio	F	Clearance
20–39 *vs* 40–59 years	< 0.05	0.07	< 0.001	> 0.2	< 0.001	< 0.05	> 0.2	> 0.2	0.06
40–59 *vs* 60–80 years	0.06	< 0.05	0.13	> 0.2	< 0.01	< 0.05	< 0.05	> 0.2	0.05
20–39 *vs* 60–80 years	> 0.2	< 0.01	< 0.001	> 0.2	< 0.001	< 0.001	< 0.01	> 0.2	< 0.001

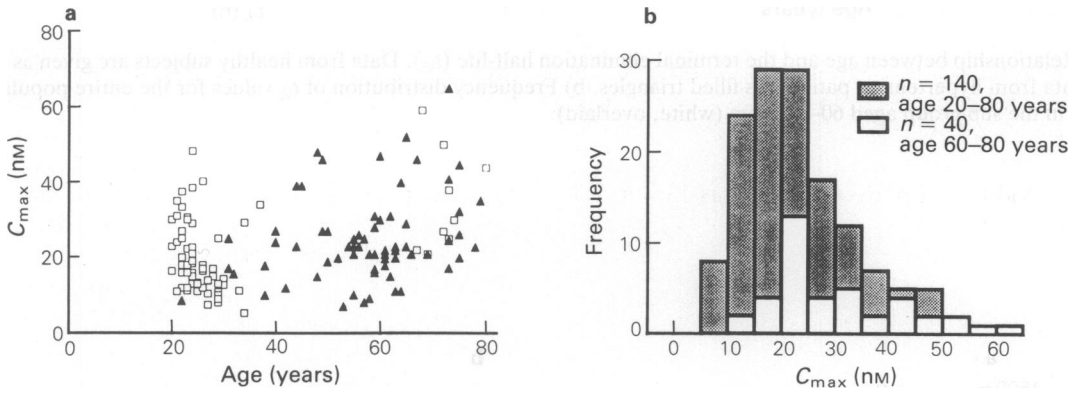


Figure 4 a) Relationship between age and maximum plasma concentrations of felodipine (C_{max}). Data from healthy subjects are given as open squares and data from hypertensive patients as filled triangles. b) Frequency distribution of C_{max} values for the entire population (hatched), and in the sub group aged 60–80 years (white, overlaid).

individual variability and overlap between age groups. The range of half-life was from 6 h up to 35 h in the youngest group and from 12 to 66 h in the eldest group. There was an increase in $t_{½}$ with age (Table 2) and the frequency distribution was slightly skewed.

Clearance Plasma clearance was calculated in the 42 individuals who received i.v. felodipine (see Figure 7). Values ranged from 106 to 1400 ml min^{-1} with an inverse relation to age. The youngest group had a mean plasma clearance of 821 ± 325 ml min^{-1} and the eldest group 448 ± 176 ml min^{-1} (Table 2). This corresponds to blood clearances of 1.2 l min^{-1} and 0.7 l min^{-1}, respectively, assuming a fixed plasma/blood drug concentration value of 0.69 (Edgar *et al.*, 1985b).

AUC The mean AUC of felodipine increased with age, but there was a considerable overlap between the age groups (Figure 8). The AUC of felodipine in the youngest group was 75 ± 34 nM h. In the middle age

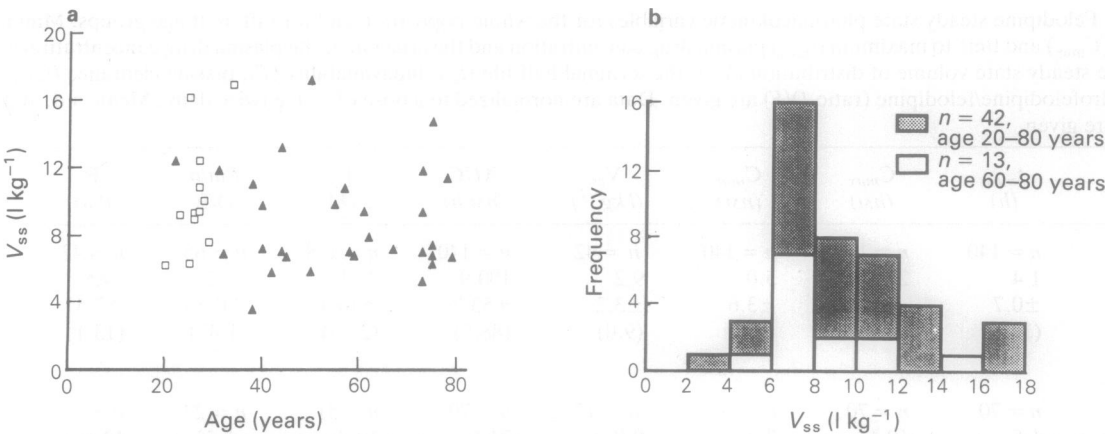


Figure 5 a) Relationship between age and the steady state volume of distribution (V_{ss}). Data from healthy subjects are given as open squares and data from hypertensive patients as filled triangles. b) Frequency distribution of V_{ss} values for the entire population (hatched) and in the sub group aged 60–80 years (white, overlaid).

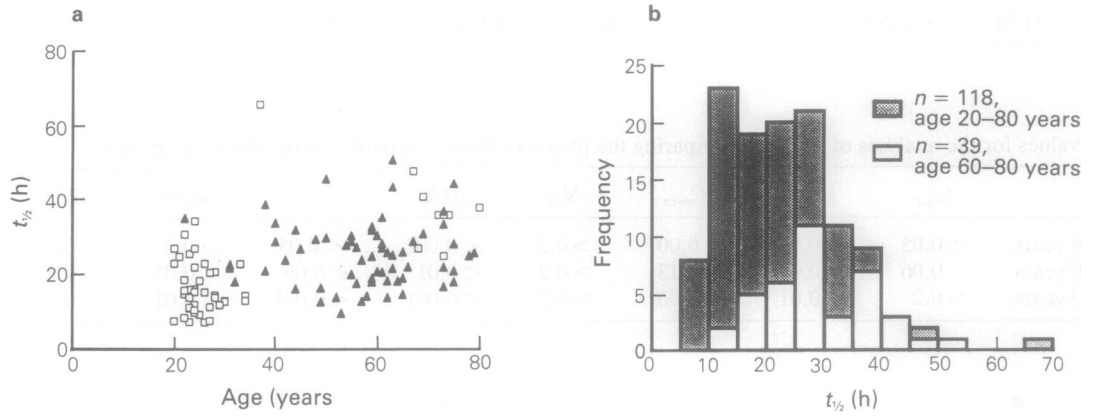


Figure 6 a) Relationship between age and the terminal elimination half-life ($t_{½}$). Data from healthy subjects are given as open squares and data from hypertensive patients as filled triangles. b) Frequency distribution of $t_{½}$ values for the entire population (hatched) and in the sub group aged 60–80 years (white, overlaid).

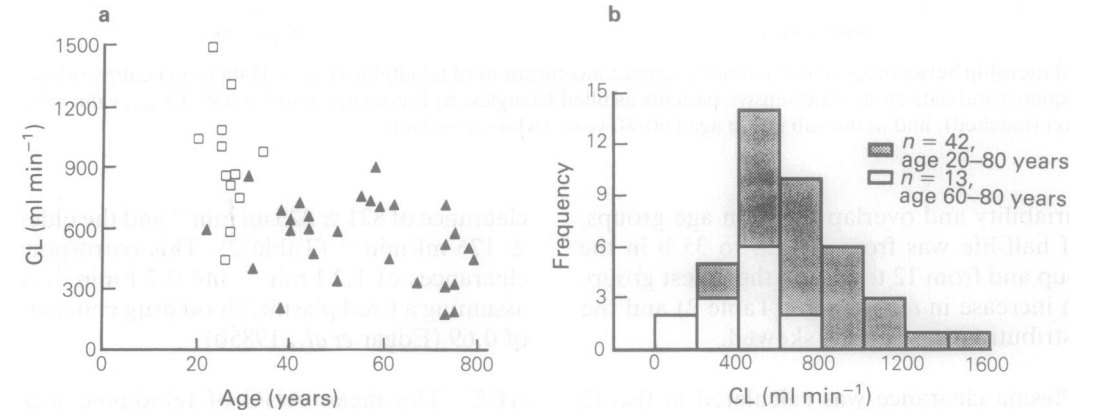


Figure 7 a) Relationship between age and the plasma clearance. Data from healthy subjects are given as open squares and data from hypertensive patients as filled triangles. b) Frequency distribution of CL values for the entire population (hatched) and in the sub group aged 60–80 years (white, overlaid).

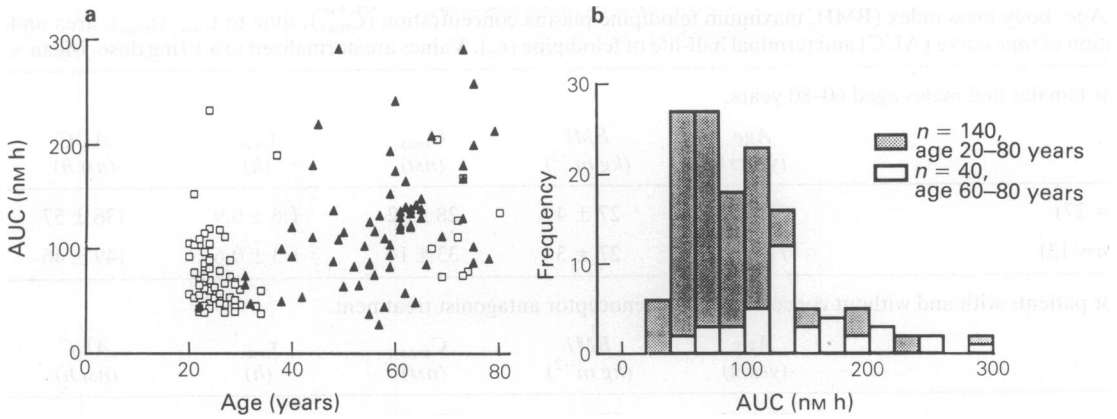


Figure 8 a) Relationship between age and the area under the plasma felodipine concentration *vs* time curve (AUC). Data from healthy subjects are given as open squares and data from hypertensive patients as filled triangles. b) Frequency distribution of AUC values for the entire population (hatched) and in the sub group aged 60–80 years (white, overlaid).

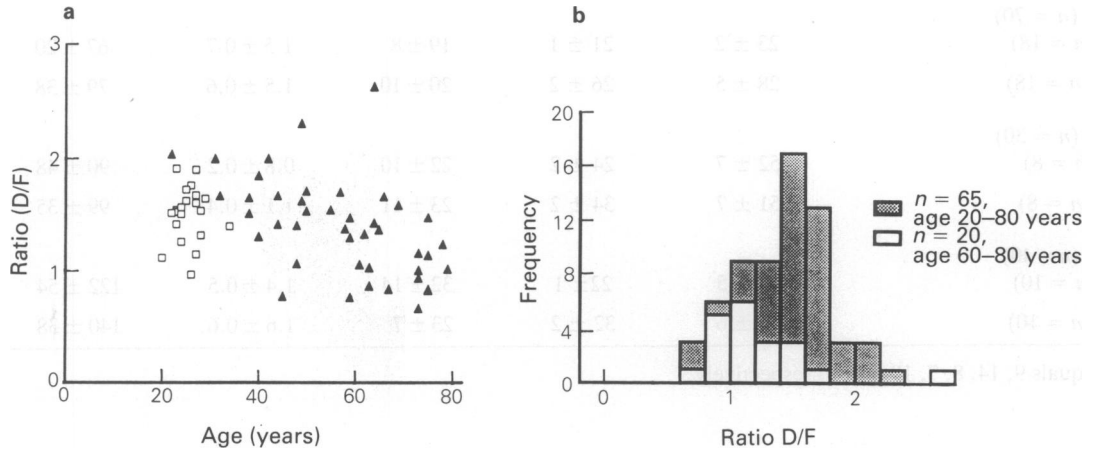


Figure 9 a) Relationship between age and the ratio of the AUC of the first metabolite of felodipine (dehydrofelodipine) to that of unchanged drug (ratio D/F). Data from healthy subjects are given as open squares and data from hypertensive patients as filled triangles. b) Frequency distribution of ratio D/F values for the entire population (hatched) and in the sub group aged 60–80 years (white, overlaid).

Table 3 Dehydrofelodipine trough (C_{min}), peak (C_{max}) and time to peak plasma concentrations and area under the plasma concentration *vs* time curve. Data are given for the whole population, and for different age groups. Data are normalized to a 10 mg twice daily dose of felodipine. Mean, s.d. and medians (in brackets) are given

	t_{max} (h)	C_{max} (nM)	C_{min} (nM)	AUC (nM h)
All	1.5 ± 0.8 (1.5)	35.6 ± 18.9 (29.6)	6.8 ± 4.6 (5.5)	142 ± 62 (130)
Age groups				
20–39 years n = 27	1.8 ± 0.8 (2.0)	27.6 ± 10.7 (26.0)	4.2 ± 1.3 (4.0)	109 ± 25 (112)
40–59 years n = 17	1.1 ± 0.5 (1.0)	46.1 ± 23.0 (37.0)	7.4 ± 5.7 (6.8)	169 ± 96 (159)
60–80 years n = 20	1.5 ± 0.8 (1.0)	37.4 ± 19.8 (34.7)	9.9 ± 4.6 (9.1)	163 ± 37 (164)

group there was an increase in the AUC to 110 ± 55 nM h and a further increase to 140 ± 54 nM h was seen in the oldest age group (Table 2). The frequency distribution of the AUC indicated a skewed distribution, with no evidence of bimodality.

The AUC values of felodipine in the young subjects ranged from 38 to 233 nM h. A similar six-fold variation between highest and lowest values was seen in the elderly although at a somewhat higher level, 49 to 290 nM h.

Metabolism Some pharmacokinetic variables for the first metabolite of felodipine (dehydrofelodipine) are given in Table 3. The ratio between the AUC values of dehydrofelodipine and felodipine could be calculated in 65 individuals (Figure 9). A negative relation to age was found. The mean value was lower in the oldest group (1.2 ± 0.4) compared with the young group (1.6 ± 0.3). The terminal half-life of felodipine was not related to this metabolite ratio. The individuals with the highest AUC of felodipine had low values of the ratio between dehydrofelodipine and felodipine.

Table 4 Age, body mass index (BMI), maximum felodipine plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration *vs* time curve (AUC) and terminal half-life of felodipine ($t_{½}$). Values are normalized to a 10 mg dose. Mean ± s.d. are given

a) Data for females and males aged 60–80 years.

	Age (years)	*BMI ($kg\ m^{-2}$)*	C_{max} *(nM)*	t_{max} *(h)*	*AUC (nM h)*	$t_{½}$ *(h)*
Males (n = 27)	67 ± 6	27 ± 4	28 ± 12	1.6 ± 0.9	136 ± 57	31 ± 10
Females (n= 13)	71 ± 6	27 ± 3	33 ± 14	1.3 ± 0.6	149 ± 46	24 ± 6

b) Data for patients with and without concomitant β-adrenoceptor antagonist treatment.

	Age (years)	*BMI ($kg\ m^{-2}$)*	C_{max} *(nM)*	t_{max} *(h)*	*AUC (nM h)*	$t_{½}$ *(h)*
No β-adrenoceptor antagonist (n = 35)	58 ± 15	27 ± 4	25 ± 13	1.3 ± 0.7	122 ± 64	25 ± 8
With β-adrenoceptor antagonist (n = 32)	56 ± 9	28 ± 4	25 ± 10	1.3 ± 0.7	123 ± 52	26 ± 10

c) Data for the highest and lowest quartiles of body mass index in each age group.

	Age (years)	*BMI ($kg\ m^{-2}$)*	C_{max} *(nM)*	t_{max} *(h)*	*AUC (nM h)*	$t_{½}$ *(h)*
20–39 years (n = 70)						
Low BMI (n = 18)	23 ± 2	21 ± 1	19 ± 8	1.5 ± 0.7	67 ± 20	15 ± 6[a]
High BMI (n = 18)	28 ± 5	26 ± 2	20 ± 10	1.5 ± 0.6	79 ± 38	25 ± 15[b]
40–59 years (n = 30)						
Low BMI (n = 8)	52 ± 7	24 ± 2	22 ± 10	0.8 ± 0.2	90 ± 48	26 ± 11[c]
High BMI (n = 8)	51 ± 7	34 ± 2	23 ± 11	1.1 ± 0.4	99 ± 35	27 ± 2[d]
60–80 years (n= 40)						
Low BMI (n = 10)	70 ± 5	22± 1	32 ± 14	1.4 ± 0.5	122 ± 54	27 ± 8[e]
High BMI (n = 10)	67 ± 6	32 ± 2	23 ± 7	1.6 ± 0.6	140 ± 38	30 ± 8[f]

[a,b,c,d,e,f]: n equals 9, 14, 8, 7, 10 and 10 respectively.

Pharmacokinetic variables in relation to other factors

The whole study population and representative sections were also analysed for possible relationships between pharmacokinetic variables and sex, body mass index as well as concomitant antihypertensive treatment (Table 4).

Female patients had somewhat lower terminal half-lives of felodipine than an age-matched group of men, whereas C_{max}, t_{max} and AUC were similar for men and women (Table 4a).

There were no differences in the AUC, C_{max}, t_{max} or $t_{½}$ of felodipine between patients who were receiving β-adrenoceptor antagonists compared with those who received felodipine alone (Table 4b).

There were no consistent differences in the pharmacokinetic variables when comparing individuals with low and high body mass indices in each age group (Table 4c).

Discussion

Most of the pharmacokinetic data from this large population support previous findings from smaller studies (Edgar *et al.*, 1987). The latter showed that felodipine is absorbed rapidly from the gastrointestinal tract when given as conventional tablets, giving peak plasma drug concentrations after 1–2 h. The fraction of the dose reaching the systemic circulation is approximately 15% and the elimination of felodipine can be described by a polyexponential function with a terminal elimination half-life of about 24 h. A steady state volume of distribution of ~9 l kg^{-1} indicate extensive extra vascular distribution of felodipine and a blood clearance of approximately 1 l min^{-1} suggests that it is a high clearance drug.

The influence of other factors, such as age, sex, body mass index, other drug therapy etc. have not been evaluated extensively. In the present study the metabolite/felodipine ratio and the clearance of felodipine were inversely related to age. The steady state volume of distribution and systemic availability were not influenced by age. The mean plasma concentrations of felodipine increased with age both at trough and peak and when measured as the area under the plasma drug concentration *vs* time curve. Although age influenced many of the pharmacokinetic variables the interindividual variability in the pharmacokinetic variables was large at any age. Therefore, age alone is a poor predictor of the pharmacokinetics of felodipine.

The study population included both normotensive individuals and patients with essential hypertension. There are well known differences between normotensives and hypertensives in the pharmacodynamic (i.e. BP and

HR) response to felodipine. In the present study the normotensive subjects dominated the youngest age group and the hypertensives the eldest group. The figures relating pharmacokinetic variables with age (Figures 4–9) show individual data, differentiating between healthy subjects and hypertensive patients. There is no suggestion from these figures that hypertensive patients should have different pharmacokinetics compared with healthy individuals indicating that the pharmacokinetic changes seen are not an effect of hypertension.

Our study population included healthy Caucasian subjects and hypertensive patients of both sexes aged 20–80 years. The study population, however, was predominantly male and no woman below the age of 50 years was included since all studies excluded women of child-bearing potential. In the relatively small female population studied, the terminal half-life of felodipine was found to be shorter than for men whereas none of the other studied variables differed between the sexes. A possible explanation of the shorter half-life is that women > 60 years all belong to studies where plasma samples only were collected up to 27 h after dose. 40% of the men in this age group had plasma samples taken for at least 48 h. This would tend to give higher values for the half-lives in the male population since there are more data points during the slowest elimination phase in this group.

The pharmacokinetics of 1,4-dihydropyridine calcium antagonists such as nifedipine and felodipine are age-related due to a reduction in clearance in the elderly (Landahl *et al.*, 1988; Robertson *et al.*, 1987). The inverse relationship between age and plasma clearance for felodipine was clearly demonstrated in our study (cf. Figure 7). The decrease in clearance and in the ratio of dehydrofelodipine/felodipine with increasing age could be caused by either a decrease in liver blood flow or a decreased metabolic capacity or a combination of the two. Hepatic blood flow has previously been shown to be age-dependently reduced in man (Wood *et al.*, 1979). Felodipine has a high plasma protein binding (> 99.5%, Regårdh *et al.*, 1989), but also a high extraction ratio (> 0.8, Edgar *et al.*, 1985a). Thus, possible changes in plasma protein binding should only have a limited influence on clearance. They could, however, have a significant effect on oral clearance.

Our population was larger and covered a wider range of ages and other background factors compared with previous studies on a possible polymorphism in the disposition of dihydropyridines (Kleinbloesem *et al.*, 1984; Renwick *et al.*, 1988; Schellens *et al.*, 1988). Our data are in accordance with the studies of Renwick *et al.* (1988) and Schellens *et al.* (1988), but at variance with the data presented by Kleinbloesem *et al.* (1984), all investigating the kinetics of nifedipine. Kleinbloesem *et al.* (1984) suggested that the bimodality of the plasma concentration of nifedipine, the urine concentration of metabolite as well as the effect on BP and HR were caused by genetic differences in the metabolic capacity. In our opinion the findings by Kleinbloesem *et al.* (1984) may have other explanations, such as too small a sample size. Nifedipine as well as felodipine is mainly oxidized by the cytochrome $P450_{IIIA}$ system (Guengerich *et al.*, 1986). If the hypothesis of Kleinbloesem *et al.* (1984) were true it would be of considerable clinical interest since $P450_{IIIA}$ oxidises not only a wide range of dihydropyridine calcium antagonists but also catalyses for example the 2- and 4-hydroxylation of 17 β-oestradiol and the 6 β-hydroxylation of testosterone (Guengerich *et al.*, 1986).

In order to disclose the possibility of phenotypic drug oxidation by the $P450_{IIIA}$ enzyme, we used the AUC of felodipine as well as the distribution of the ratio metabolite/drug AUC-values. Jackson *et al.* (1986) suggested that the use of metabolite/drug ratio, estimated from the AUC of the urine concentration, is one of the most valid methods to study oxidation in phenotypes. Since no unchanged felodipine has been found in urine we studied felodipine and its first metabolite (inactive) in plasma. Both the evaluation of the AUC of felodipine and the metabolite/drug ratio failed to separate any clear group of individuals. However, we cannot fully exclude the existence of poor metabolizers in a small proportion of the population.

In conclusion, the present study provides evidence for an age-related disposition of felodipine. This age-related change is most likely due to a reduction of hepatic clearance with increasing age. In our study population, covering a wide range of Caucasian individuals, there was no indication of polymorphism in felodipine pharmacokinetics. The relevance of the age-dependent pharmacokinetics of felodipine for the treatment of patients with hypertension and/or other cardiovascular diseases is, however, limited due to the fact that there is a large variation in kinetics between subjects of similar age. This further emphasizes the importance of individual dose titration of felodipine.

We thank Dr Lars Johansson and his co-workers for assaying felodipine and its metabolite, and all the investigators (see below) and their staff who helped us to perform the studies. We would also like to thank Ms Catherine Kristersson for helping us with data entry.

Participating investigators:

Per Collste	Thomas Hedner	Philip Routledge
Dag Elmfeldt	Asger Heggelund	Ola Rönn
Keith Eliasson	Britta Hylander	Cameron Swift
Margaretha Grind	Sten Landahl	Steve Warrington
Kjell Haglund	Bodil Lernfeldt	
Birgitta Hasselgren	Per Lundborg	

References

Ahnoff, M. (1984). Determination of felodipine in plasma by capillary gas chromatography with electron capture detection. *J. Pharm. Biomed. Anal.*, **2**, 519–526.

Ahnoff, M., Ervik, M. & Johansson, L. (1987). Comparison of high-selectively gas chromatographic methods, including column switching, for the determination of felodipine in plasma. *J. Chromatogr.*, **394**, 419–427.

Blychert, E., Hedner, T., Dahlöf, C. & Elmfeldt, D. (1990). Plasma-concentration effect relationships of intravenous and extended release oral felodipine in hypertensive patients. *J. cardiovasc. Pharmac.*, **15**, 428–435.

Bäärnhielm, C., Skånberg, I. & Borg, K. O. (1984). Cytochrome P-450 dependent oxidation of felodipine—a 1.4-dihydropyridine—to the corresponding pyridine. *Xenobiotica*, **14**, 719–726.

Edgar, B., Hoffman, K. J., Lundborg, P., Regårdh, C. G., Rönn, O. & Weidolf, L. (1985b). Absorption, distribution and elimination of felodipine in man. *Drugs*, **29** (Suppl. 2), 9–15.

Edgar, B., Lundborg, P. & Regårdh, C. G. (1987). Clinical pharmacokinetics of felodipine—a summary. *Drugs*, **34** (Suppl. 3), 16–27.

Edgar, B., Regårdh, C. G., Johnsson, G., Johansson, L., Lundborg, P., Löfberg, I. & Rönn, O. (1985a). Felodipine kinetics in healthy men. *Clin. Pharmac. Ther.*, **38**, 205–211.

Guengerich, F. P., Martin, M. V., Beaune, P. H., Kremers, P., Wolff, T. & Waxman, D. J. (1986). Characterisation of rat and human liver microsomal cytochrome P-450 forms involved in nifedipine oxidation, a prototype for genetic polymorphism in oxidative drug metabolism. *J. biol. Chem.*, **261**, 5051–5060.

Hoffman, K. J. & Andersson, L. (1984). Metabolism of [^{14}C]felodipine—a new vasodilating drug—in healthy men. *Drugs*, **34** (Suppl. 3), 43–52.

Jackson, P. R., Tucker, G. T., Lennard, M. S. & Woods, H. F. (1986). Polymorphic drug oxidation: pharmacokinetic basis and comparison of experimental indices. *Br. J. clin. Pharmac.*, **22**, 541–550.

The Joint National Committee (1988). The 1988 report of the Joint National Committee on detection, evaluation and treatment of high blood pressure. *Arch. intern. Med.*, **148**, 1023–1038.

Kleinbloesem, C. H., Van Brummelen, P., Faber, H., Danhof, M., Vermeulen, N. P. E. & Breimer, D. D. (1984). Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. *Biochem. Pharmac.*, **33**, 3721–3724.

Landahl, S., Edgar, B., Gabrielsson, M., Larsson, M., Lernfeldt, B., Lundborg, P. & Regårdh, C. G. (1988). Pharmacokinetics of felodipine in elderly hypertensive patients—a comparison with young healthy subjects. *Clin. Pharmacokin.*, **14**, 374–383.

Regårdh, C. G., Bäärnhielm, C., Edgar, B. & Hoffman, K. J. (1990). Pharmacokinetics and biotransformation of 1,4-dihydropyridine calcium antagonists. In *Progress in Drug Metabolism*, vol **12**, ed Gibson, G. G. London: Taylor and Francis Ltd.

Regårdh, C. G., Edgar, B., Olsson, R., Kendall, M., Collste, P. & Shansky, C. (1989). Pharmacokinetics of felodipine in patients with liver disease. *Eur. J. clin. Pharmac.*, **36**, 473–479.

Renwick, A. G., Robertson, D. R. C., Macklin, B., Challenor, V., Waller, D. G. & George, C. F. (1988). The pharmacokinetics of oral nifedipine—a population study. *Br. J. clin. Pharmac.*, **25**, 701–708.

Robertson, D. R. C., Waller, D. G., Renwick, A. G. & George, C. F. (1987). Age related changes in the pharmacology of nifedipine. *Br. J. clin. Pharmac.*, 244–245.

Schellens, J. H. M., Soons, P. A. & Breimer, D. D. (1988). Lack of bimodality in nifedipine plasma kinetics in a large population of healthy subjects. *Biochem. Pharmac.*, **37**, 2507–2510.

Weiss, Y. A., Safar, M. E., Lehner, J. P., Levenson, J. A., Simon, A. & Alexandre, J. M. (1978). Propranolol clearance, an estimation of hepatic blood flow in man. *Br. J. clin. Pharmac.*, **5**, 457–460.

WHO/ISH Guidelines (1989). Guidelines for the management of mild hypertension: memorandum from a WHO/ISH Meeting. *J. Hypertension*, **7**, 689–693.

Wood, A. J. J., Vestal, R. E., Wilkinson, G. R., Branch, R. A. & Shand, D. G. (1979). Effect of aging and cigarette smoking on antipyrine and indocyanine green elimination. *Clin. Pharmac. Ther.*, **26**, 16–20.

(Received 6 July 1990, accepted 24 August 1990)